WO 01/08673 PCT/US00/20834

## What is claimed is:

1. A method of treating a disease or disorder characterized by an abnormal bone or mineral homeostasis which comprises administering to a subject in need of

- 5 treatment thereof an effective amount of a calcilytic compound in conjunction with an effective amount of an anti-resorptive agent.
  - 2. A method according to claim 1 wherein the calcilytic compound is selectedfrom the group consisting of:

N-[(2R-Hydroxy-3-[(3-chloro-2-cyano)phenoxy-propyl]-1,1-dimethyl-2-(2-

- 10 naphthyl)ethyl amine hydrochloride;
  - N-[(2R-Hydroxy-3-[(3-chloro-2-cyano)phenoxy-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl amine hydrochloride;
  - N-[(2R-Hydroxy-3-[(2,3-dichloro)phenoxy-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl amine hydrochloride;
- N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(6-(1,2,3,4-tetrahydronaphthyl)ethylamine;
  N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(Benzothien-3-yl)-ethylamine;
  N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-
- phenoxy]propyl]-1,1-dimethyl-2-(Benzothien-2-yl)-ethylamine;
  N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(decahydronapthalen-2-yl)ethylamine;
  N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-4-phenylbutylamine;
- N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-4-(2-methoxyphenyl)butylamine;
  N-[2R-Hydroxy-3-[[2-cyano-4-[N-methyl-N-[4-ethylcarboxyphenyl]sulfonyl]-amino]phenoxy]propyl]-1,1-dimethyl-2-(2-napthyl)ethylamine;
  N-[2R-Hydroxy-3-[[2-cyano-4-[N-methyl-N-[3-
- 30 methylcarboxymethoxyphenyl]sulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(2-napthyl)ethylamine;

WO 01/08673 PCT/US00/20834

N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-2-[2-napthyl]ethylamine;
N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(1,2,3,4-tetrahydronaphth-6-

- yl)ethylamine.

  N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(benzothien-3-yl)-ethylamine;

  N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(benzothien-2-yl)-ethylamine;
- N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-2-(decahydronapthalen-2-yl)ethylamine;
  - N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-4-(2-
- 15 methoxyphenyl)butylamine;
  N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methylsulfonyl]-N-[[[1-[2-[6-methyl]amino]-pyridyl]ethyl]amino]phenoxy]propyl]-1,1-dimethyl-4-phenylbutylamine;
  N-[2R-Hydroxy-3-[[2-cyano-4-[N-benzyl-N-[4-methylphenyl]sulfonyl]amino]
  phenoxy]propyl]-1,1-dimethyl-2-[4-methoxyphenyl]ethylamine;
- N-[2R-Hydroxy-3-[[2-cyano-4-[N-[4-benzyl]sulfonyl]amino]
  phenoxy]propyl]-1,1-dimethyl-2-[2-napthyl]ethylamine;
  N-[2R-Hydroxy-3-[[2-cyano-5-[[4-carboxy]phenyl]phenoxy]propyl]1,1-dimethyl-2-[napthyl]ethylamine;
  N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methyl-N-[3-carboxyl]phenyl]sulfonyl]amino]-
- phenoxy]propyl]-1,1-dimethyl-2-[2-napthyl]ethylamine; N-[2R-Hydroxy-3-[[2-cyano-4-[[N-methyl-N-[3-methylcarboxyl]phenyl]sulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-[2-napthyl]ethylamine;
- N-[2R-Hydroxy-3-[[2-cyano-4-(2-phenyl-2-R,S-carboxyl)phenoxy]-propyl]-1,1-30 dimethyl-2-(2-naphthyl)ethylamine;

WO 01/08673 PCT/US00/20834

N-[2R-Hydroxy-3-[[2-cyano-4-(3-carboxypropyl)phenoxy]-propyl]-1,1-dimethyl-2-naphthylethylamine;

(N-[2R-Hydroxy-3-[[2-cyano-5-(3-carboxypropyl)phenoxy]-propyl]-1,1-dimethyl-2-naphthylethylamine; and

- 5 (N-[2R-Hydroxy-3-[2-[6-aminomethyl]pyridyl]ethyloxy]-1,1-dimethyl-2-naphthylethylamine.
  - 3. A method according to claim 2 wherein the anti-resorptive agent is selected from the group consisting of: estrogen, 1, 25 (OH)<sub>2</sub> vitamin D3, calcitonin, selective estrogen receptor modulators, vitronectin receptor antagonists, V-H+-ATPase inhibitors, src SH2 antagonists, bisphosphonates and cathepsin K inhibitors.
  - 4. A method according to claim 1 wherein the bone or mineral disease or disorder is selected from the group consisting of: periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia of malignancy, metastatic bone disease, joint replacement and osteoporosis.
- 15 5. A method according to claim 3 wherein the bone or mineral disease or disorder is osteoporosis.
  - 6. A method according to claim 1 wherein the calcilytic agent causes an increase in serum PTH levels of 3-fold or higher.
- 7. A method according to claim 1 wherein the calcilytic agent causes an
   20 increase in serum PTH levels of 2-fold or higher.
  - 8. A method of treating a disease or disorder characterized by an abnormal bone or mineral homestasis which comprises administering to a subject in need of treatment thereof an effective amount of an anabolic compound in conjunction with an effective amount of an anti-resorptive agent.

25

10